Cell Stem Cell
Industry Progress

Cell Therapy Companies Make Strong Progress from October 2012 to March 2013 Amid Mixed Stock Market Sentiment

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During Q4 2012 and Q1 2013, the cell therapy industry made strong progress in translation and commercialization. Continued development of the companies included in a dedicated stock market index suggests emergence of this industry as a distinct healthcare sector.

This Industry Progress update covers developments for publicly traded cell therapy companies with market capitalizations (market caps) greater than $50M for the period ranging from October 1, 2012 to March 31, 2013. We discuss external influencing factors affecting the industry and significant news from the companies during the period, and we present the stock market activity of their shares in the form of a dedicated index, the Cell Therapy Index (CTI), to give an indication of the financial progress of the sector overall.

Major External Influences

Federal Funding for Human Embryonic Stem Cell Research

On January 7, 2013, the US Supreme Court decided not to hear the appeal of the case of Sherley versus Sebelius. As is the custom for the Supreme Court, no reason was given. The origin of the lawsuit was targeted at the guidelines issued by the National Institutes for Health (NIH) in July 2009 implementing President Obama's executive order, "Removing Barriers to Responsible Scientific Research Involving Human Stem Cells," which lifted some of his predecessor's restrictions on federal funding for human embryonic stem cell (hESC) work. Sherley initially won a preliminary injunction against the NIH. However, the trial court and later the appeals court ruled in the NIH's favor. The final petition to the Supreme Court was denied, thus bringing to a close the 3 year legal battle challenging the legality of funding hESC research by the NIH (Baker, 2013). Industry and academia have welcomed this news because it removes uncertainty about a large pool of existing and future research.

Patenting of hESCs in Europe

In the case of Oliver Brüstle versus Greenpeace, relating to the patentability of neural precursor cells derived from hESCs, the Court of Justice of the European Union (CJEU) ruled in late 2011 that, "a process which involves removal of a stem cell from a human embryo at the blastocyst stage, entailing the destruction of that embryo, cannot be patented." This ruling created uncertainty for hESC-based companies and cast a shadow over the technology with concerns that there might be a much larger knock-on effect. However, on November 27, 2012 the Bundersgerichtshof, the German court that had originally referred the legal questions to the CJEU, applied the CJEU ruling narrowly, thereby enabling inventors to be granted patents over hESC-derived cell technologies that (1) do not directly involve embryo destruction (effectively the practice of the UK Intellectual Property Office) and/or (2) expressly exclude ("disclaim") destructive uses of human embryos even if there were no such nondestructive uses at the application date. It remains to be seen whether other EU Member States will adopt a similar approach, but if they do, the impact of the original CJEU ruling could well be significantly curtailed.

UK Cell Therapy Catapult

Funded with $110M of public funds via the Technology Strategy Board, the Cell Therapy Catapult has been established at Guy's Hospital, London. The Catapult is focused on bridging the gap between academic discoveries and the point where they are investment ready—typically at the end of a successful phase 2 clinical trial. An internationally respected senior management team is now in place and the first corporate deals are starting to emerge. The initial commercial collaboration is an R&D program with ReNeuron (Guildford, UK) to work on new manufacturing technologies and assays in order to advance ReNeuron's lead stem cell therapy (CTX). CTX is already progressing in a phase 1 trial for stroke and is also shortly to enter a trial for critical limb ischemia. The Catapult will contribute $2M to the collaboration in the form of expert knowledge, access to state-of-the art facilities, and equipment.

California Institute for Regenerative Medicine

In response to the critical review of the California Institute for Regenerative Medicine (CIRM) carried out by the Institute of Medicine at CIRM's request, its Governing Board has proposed a number of major changes across multiple areas including increased involvement with industry. The report, published in December 2012, acknowledged the many achievements of CIRM, including establishing California as an international hub of stem cell R&D, but also identified

key areas for urgent improvement including the need for an external scientific advisory board, resolution of the perceived conflicts of interest on its governing board, and reorganization to ensure that the board is able to provide independent oversight (DeFrancesco, 2013a).

In January 2012, an independent economic impact study by the Berkeley Research Group focusing on the first $1.5B of CIRM's grant funding reported that it "is generating 38,000 job years and $286M in new tax revenue in the state through 2014." However, 13,000 of the jobs are in the construction and building trades. The report does not measure the economic impact of stem-cell-based companies that have opened facilities or expanded in the state as a direct result of CIRM's activities. The report states that it is too early to quantify CIRM's impact on the traditional biotech clusters (the Bay Area and San Diego), but notes that, "industries participating in a strong cluster register higher employment growth, as well as higher wages, number of establishments, and patenting." An example given is ViaCyte (San Diego, CA, USA), who have had a 45% growth in their headcount to over 50 staff since receiving their first CIRM grant in 2009.

CTI

Globally there are between 300 and 700 companies actively progressing cell-based therapies, ranging from small university spinouts to multinational companies such as GlaxoSmithKline, Johnson & Johnson, Pfizer, and Sanofi (Genzyme). If one excludes the larger pharmaceutical, biologics, and/or medical device companies, there are around 50 publicly traded companies of various different sizes that focus predominantly on cell-based approaches (Mason et al., 2012).

In a previous article, we outlined the application of a bespoke stock index of cell therapy companies to monitor the overall growth and volatility of this industry sector (Brindley et al., 2011). To produce a fair representation of an industry overall and to damp down excessive volatility, it is conventional to calculate aggregated indices of only the companies with market caps greater than a value appropriate for the specific industry. Given the very large spread of market caps for cell therapy companies, we selected a cutoff of $50M for compiling a new CTI. On October 1, 2012, this cut off resulted in 25 companies being included to form the CTI. Table S1 shows a list of the companies together with a brief description of their technologies and regulatory approved products. Due to the large range of values for the market caps and share prices, the market caps are weighted, and the percentage change in the closing price of the share each day compared to the initial price on the starting date is used to calculate the CTI.

Similarly to the situation seen in a previous analysis (Brindley et al., 2011), individual share prices and the index value overall showed significant variation during the 6 month period following October 1, 2012. For example, the aggregated market cap dropped from over $7B on October 1, 2012 to approximately $6B on January 1, 2013, finally recovering to just over $7B by March 31, 2013. It is of note that for each of these time points, Mesoblast was a predominant force, contributing to one-third of the loss in Q4 2012 and half of the gain in Q1 2013. Mesoblast is a bellwether stock in the sector. The share price falls were due to rumors about when, and even if, Mesoblast and its strategic partner, Teva Pharmaceuticals, would start its phase 3 congestive heart failure trial (which were proven unfounded in November 2012), and rumors of a new financing of $180M that probably negatively impacted the share price in the months preceding the March 2013 raise.

The cell therapy industry can be considered a fourth pillar of therapeutic healthcare, complementing the medical device, pharmaceutical, and biotechnology sectors (Mason et al., 2011). However, investors frequently group cell therapy together with biotechnology, so we have also plotted two of biotech's most trusted indices (NYSE Arca Biotechnology Index [BTK] and Nasdaq Biotechnology Index [NBI]) alongside the CTI to enable comparison. It is important to note the substantial difference in the maturity of the two industries, i.e., of fledgling companies with no/little revenue versus predominantly small and large cap companies, several with billion dollar revenues. The NBI consists of both biotechs and pharmaceutical companies. It is calculated using a modified capitalization-weighted methodology from companies with a market cap of at least $200M. It covers approximately 120 companies, a few of which focus on cell-based therapy, such as Cytori Therapeutics, Dendreon, and Osiris Therapeutics (Thomas, 2012). The BTK is an equal dollar weighted, concentrated index of 20 large biotechnology stocks and also includes Dendreon.

During the period from October 1, 2012 to March 31, 2013, the CTI behaved very differently from the biotech indices (Figure 1), confirming our earlier observation that the cell therapy sector is a unique and distinct investment class relative to biotech (Brindley et al., 2011). During Q4 2012 the CTI lost around 20% of its value and then proceeded to a near-full recovery. For the same period, the BTK and NBI also initially lost value early on, but recovered earlier and underwent steady growth from November 2012 onward. The major gains in the NBI and BTK are seen as an extension of the investor confidence in the biotech sector seen virtually throughout 2012. Highlights for the period included eight new drugs being approved for marketing by the FDA in December, bumping the total number of drug approvals for the calendar year to 37, the largest number of approvals since 1996 (Osborne, 2013). This momentum has continued: within a couple of months of the start of 2013, six further drugs had received FDA approval (DeFrancesco, 2013b). The biotech indices also outperformed the general markets last year, as investors enthusiastically accumulated shares in the larger market cap companies, including Amgen, Biogen Idec, and Gilead Sciences, the three of which produced close to $60B in combined shareholder gains during 2012 (Yang, 2013).

News for Companies in the CTI

Aastrom Biosciences, in response to financial constraints, made a strategic shift to focus solely on their phase 2b ixmyelocel-T trial for dilated cardiomyopathy and to stop the phase 3 critical limb ischemia study.

Advanced Cell Technology's independent Data and Safety Monitoring Board, which oversees the clinical trials in the US and EU for Stargardt's macular dystrophy and dry age-related macular degeneration, has authorized an increase

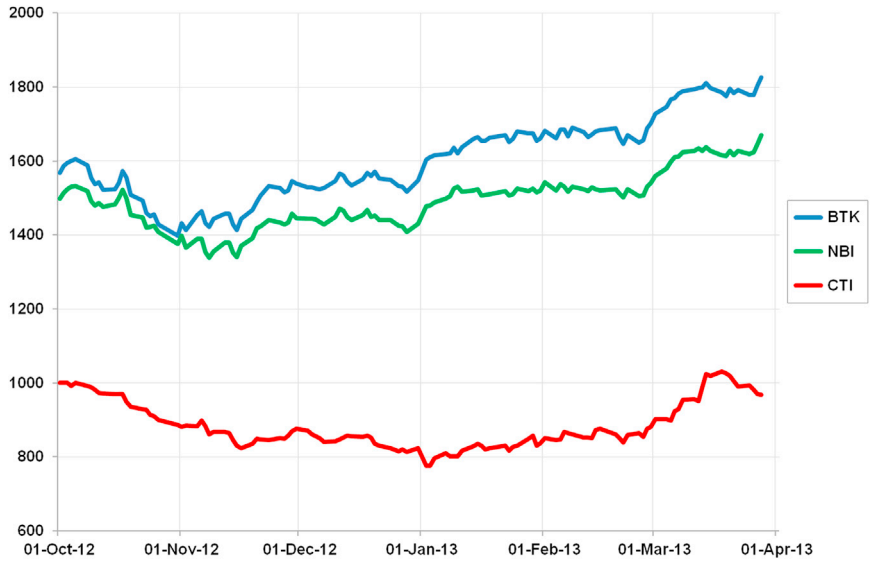

Figure 1. Cell Therapy Index for Q4 2012 and Q1 2013
The index is composed of cell therapy companies with market capitalizations greater than $50M. It commences on October 1, 2012 with a benchmark value set at 1,000. The major established biotechnology indices (BTK and NBI) are included and demonstrate that the cell therapy industry is a unique investment class and thus distinct from biotech. See also Table S1.

in cell dose for the next patient cohorts to 150,000 hESC-derived retinal pigment epithelial cells.

Athersys was named for a second year in Deloitte's Technology Fast 500, a ranking of the 500 fastest growing technology, media, telecommunications, life sciences, and clean technology companies in North America. Athersys' revenues grew 217% during the year.

Bionet's data for 2011 shows sales revenues of $20M, of which 94% was from cord blood banking operations. Bionet subsidiary *Genesis Genetics Asia* made its initial public offering on the Gre Tai Securities Market (Taiwan). This is the country's first publicly traded company specialized in providing genetic testing, databases, and informatics services to the life sciences industry.

BioTime subsidiary *Asterias Biotherapeutics* (formerly *BioTime Acquisition Corporation*, Menlo Park, CA, USA) agreed to acquire *Geron*'s (CA, USA) hESC programs including intellectual property, cell lines, and a phase 1 clinical trial for spinal cord injury, in exchange for $5M cash, 9M BioTime shares, and warrants. Geron will be entitled to royalties on future commercial products.

China Cord Blood Corporation (CCBC), China's largest cord blood bank, was granted American Association of Blood Banks (AABB) Accreditation for its Beijing subsidiary. AABB is an international, not-for-profit association dedicated to the advancement of science and the practice of blood centers and transfusion medicine. It is committed to developing and delivering standards, accreditation, and educational programs.

Cordlife Group and CCBC have formed a strategic partnership. As a result, CCBC now wholly owns Guangzhou Municipality Tianhe Nuoya Bio-engineering Company, a cord blood banking operator in Guangdong (Canton) province, in exchange for 10% of CCBC.

Cytomedix will collaborate with the NIH on a phase 2 trial for intermittent leg claudication. Funded by NHLBI/NIH and managed by the Cardiovascular Cell Therapy Research Network (consisting of seven US centers), the study is an 80 patient, double-blind, placebo-controlled trial intended to demonstrate the safety and efficacy of Cytomedix's ALD-301 cells.

Cytori Therapeutics lost its appeal to the US Court of Appeals regarding the FDA's decision that the Celution cell processing technology was not substantially equivalent to the cited predicate devices required for 510(k) approval. Cytori will instead seek regulatory approval via the Premarket Approval (PMA) route with cardiac disease trials that are already underway.

Dendreon sold its immunotherapy manufacturing facility at Morris Plains (NJ, USA) to Novartis for $43M. The 173,000 square foot state-of-the-art cell processing facility was built for manufacturing Provenge (sipuleucel-T). Dendreon had already announced its intent to wind down Morris Plains as part of a restructuring plan.

Fibrocell Science's phase 2 study to evaluate the safety and efficacy of LaViv (azficel-T) for the treatment of moderate-to-severe acne scars has been accepted for publication in Dermatologic Surgery. LaViv therapy was associated with clinically meaningful improvement in acne scar appearance and was judged safe and superior to control treatment.

ImmunoCellular Therapeutics had its investigational new drug (IND) application allowed by the FDA for ICT-140, a dendritic cell vaccine targeting seven antigens that are overexpressed in ovarian cancer and cancer stem cells. This safety study will enroll approximately 20 patients who have previously been treated with standard chemotherapy.

Japan Tissue Engineering Company (J-TEC) is now reimbursed for JACC (autologous cultured cartilage) for traumatic knee cartilage deficiency and osteochondritis dissecans from Japan's medical insurance system. Osteoarthritis was excluded from the indications. The insurance-reimbursed price is ¥2M (~$21,000) including tax. JACC received Japanese regulatory approval (Ministry of Health, Labour and Welfare) in 2012.

Medipost started a phase 1/2a trial in North America of Cartistem for cartilage regeneration—the first time a cell therapy approved by the Korean Food and Drug Administration has entered trials in the USA. The 12 patient study is at Rush University's Hospital, Chicago, and Brigham and Women's Hospital, Massachusetts.

Mesoblast has been granted by the US Patent Office Patent 8,367,405 (isolation of adult multipotential cells by tissue nonspecific alkaline phosphatase), which confers the company with exclusive rights through March 2029 to compositions of matter covering its current products. Claims include a method of enriching for adult STRO-1+ multipotential cells.

NeoStem was ranked number one in the Tri-State region and number seven

nationally on Deloitte's 2012 Technology Fast 500.

Neuralstem received FDA approval for a phase 1 trial in chronic thoracic spinal cord injury with an American Spinal Injury Association "A" level of impairment (complete paralysis). Eight patients will receive six injections in/around the injury. Half the patients will receive 100,000 cells per injection, and if safe and tolerated, the dose will be ramped up to 200,000.

NewLink Genetics reported phase 1 dose escalation data for HyperAcute prostate cancer immunotherapy (published in the Journal of Immunotherapy). Eight patients received 12 intradermal vaccinations at doses ranging from 30–500M cells. The study demonstrated safety and evidence of vaccine-induced immunologic responses in patients, suggesting the potential for a larger study.

Northwest Biotherapeutics Chairman and CEO Linda Powers rang Nasdaq's opening bell to celebrate the company's uplisting to the Nasdaq Capital Market. The company completed major related financial accomplishments to strengthen their balance sheet by removing over $35M of debt and closing on $14M in new equity investment.

Osiris Therapeutics established its own direct sales force for Grafix, a 3D cellular matrix for serious wounds. Osiris had earlier (May 2012) announced that it had received transitional passthrough status from the Center for Medicare & Medicaid Services, with C-Codes being designated for Grafix, thus facilitating reimbursement when used in Medicare patients.

Pharmicell will merge with its wholly owned subsidiary, *ID Biochem* (Ulsan, Korea), to improve synergy between the two companies. ID Biochem is a producer of nucleosides (used for molecular diagnostics and gene therapy), methoxy polyethylene glycol (mPEG) for pharmaceuticals, and drug intermediates. It supplies mPEG to multinationals such as Merck.

Pluristem Therapeutics' licensee, United Therapeutics (Silver Spring, MD, USA), plans phase 1 studies using Pluristem's PLacental eXpanded (PLX-PAD) cells in pulmonary arterial hypertension (PAH). Under the licensing agreement, United Therapeutics will develop, market, and sell PLX-PAD cells for PAH. Pluristem received a $7M upfront payment, plus potentially up to $48M in milestone installments.

Prima BioMed announced that the Saxony Development Bank (Dresden, Germany) approved a €3.8M (~$5M) grant to support CVac development. The award will cofund phase 2 clinical trials in three new cancer indications and cofund several manufacturing optimization programs to improve the efficiency and commercial scale-up of production of their cancer cell vaccine.

StemCells will receive $19M from CIRM to help fund an IND application for Alzheimer's disease. The funding, in the form of a forgivable loan, was awarded under CIRM's Disease Team Therapy Development Award program, for preclinical development and IND-enabling activities.

TiGenix has obtained from the Spanish health authorities national reimbursement for its cartilage therapy ChondroCelect. Spain is the second country in Europe to provide national reimbursement for ChondroCelect; the first was the Netherlands in June 2012. TiGenix continues to work on obtaining national reimbursement in other European countries.

Summary of Q4 2012 and Q1 2013 Activity

Overall the major news from the CTI companies is very positive, with strong progress being made in an assortment of clinical indications, many for significant unmet medical needs. The new CTI represents the start of an ongoing process and will build over time. The BTK and NBI were established in 1991 and 1993, respectively, and have shown the most significant overall gains from 2009 onward. In comparison, the cell therapy sector is still very early in its development cycle, and therefore has real potential for major growth. We will regularly update and analyze the CTI so it can be used as a performance indicator for the global cell therapy sector.

SUPPLEMENTAL INFORMATION

Supplemental Information for this article includes one table and can be found with this article online at http://dx.doi.org/10.1016/j.stem.2013.05.017.

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